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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/780,953	02/09/2001	Manikkam Suthanthiran	955-3P/CON	1712

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EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 01/13/2004

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/780,953	SUTHANTHIRAN ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-25,27,30 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-25,27,30 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,5*.
4) ☒ Interview Summary (PTO-413) Paper No(s). *15,16*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. New grounds of rejection are presented below. Therefore, the finality of the previous Office action is hereby withdrawn. Applicant's submission after final filed on September 29, 2003 has been entered.

2. Claims 21-25, 27, 30, and 31 are pending and examined on the merits.

3. The declaration filed under 37 CFR 1.131 filed September 29, 2003 is acknowledged.

4. The election of species requirement set forth in Paper No. 7, is withdrawn upon further consideration.

Claim Rejections Withdrawn:

5. The rejection of claims 21-23 and 30 under 35 U.S.C. 103(a) as being unpatentable over Hutchinson (Hutchinson, Rev. in Immunogenetics, 1: 323-333, 1999) is withdrawn in view of the declaration.

6. The rejection of claims 21-23 and 31 under 35 U.S.C. 103(a) as being unpatentable over Ader (Ader, Curr. Opin Nephrol. Hypertens., 7: 539-545, 1998) in view of Hutchison (supra) is withdrawn in view of the declaration.

7. The rejection of claims 21-25, 27 and 30 under 35 U.S.C. 103(a) as being unpatentable over Novak (Novak, Nature Medicine, 5(4): 382, 1999, April) in view of Ohmori (Experimental Cell Research, 245: 350-359, 1998) is withdrawn in view of the declaration.

New Grounds of Rejection:

8. Claims 21-25, 27, 30 and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification fails to reasonably provide enablement commensurate with the scope of the claimed invention. The specification does not enable one skilled in the art to which the claimed invention pertains, or with which it is most nearly connected, to make and use the full scope of the claimed invention.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

The claimed inventions are drawn to compositions comprising a TGF-β antagonist and an immunosuppressive agent. In narrower embodiments, the TGF-β antagonist may be an anti-TGF-β antibody or an antigen-binding fragment thereof. The TGF-β antagonist may inhibit the activity of TGF-β1, TGF-β2 or TGF-β3; or may inhibit the activity of more than one isoform of TGF-β. Preferred examples of immunosuppressive agents are cyclosporine or FK506. The rationale provided in the specification for making and using the claimed compositions is that

cyclosporine, an example of an immunosuppressant, is a compound that appears to play a role in the promotion of tumor metastasis; and that this is caused by the production of either TGF-β1, TGF-β2 or TGF-β3. Therefore, in situations where an immunosuppressant therapy is required, one would want to also administer a TGF-β antagonist.

The specification fails to define the TGF-β antagonist as relating only to TGF-β1, TGF-β2 or TGF-β3, and therefore, the term "TGF-β antagonist" is interpreted as an antagonist of any member of the TGF-β family. The TGF-β family encompasses a large family of proteins that have varying biological functions (see Massague, J., Annu. Rev. Biochem. 67: 753-791 1998; page 754 and Table 1), and in some cases, the biological function is dependent on cell-type. Therefore, a TGF-β antagonist would be a compound that would be useful in antagonizing a wide variety of biological activities, depending on the tissue it was administered to and depending on which family member or members it antagonized.

In contrast to the wide scope of the term TGF-β antagonist, is the narrow scope of the description provided by the application, in which one anti-TGF-β antibody that binds to TGF-β1, TGF-β2 and TGF-β3 is used. In the working examples, data is provided that demonstrates that an antibody, which binds TGF-β1, TGF-β2 and TGF-β3, reduces the pro-metastatic effects of cyclosporine. Thus, while the examples provided in the specification provide one with enough information for using a composition comprising an antibody that binds to TGF-β1, TGF-β2 and TGF-β3, these examples fail to enable one to know how use a composition comprising any other possible TGF-β antagonist with any other immunosuppressants. This is because the examples fail to demonstrate whether the effects mediated by the antibody are specific to any one of TGF-β1, TGF-β2 or TGF-β3, or if the effects are mediated by a combination of all three or a subset of

TGF-β1, TGF-β2 and TGF-β3, and whether the pro-tumor properties of cyclosporine are mediated by any other TGF-β family member; and also because it is not clear that all immunosuppressants are pro-metastatic. Further, the data do not provide any evidence that FK-506 is a pro-metastatic immunosuppressant, and the data do not teach how to use any TGF-β antagonist in combination with FK-506. Therefore, one of skill in the art would not know how to use a composition comprising any TGF-β antagonist in combination with FK-506.

In view of the wide variety of biological functions of each of the members of the TGF-β family, it would not be predictable that antagonists to any one of these compounds would have the same effects in combination with cyclosporine as that of the one antibody that was used in the working example, for the purpose of inhibiting tumor metastasis. Furthermore, the specification fails to show any evidence that the pro-tumor effects of cyclosporine are predictably extended to any other immunosuppressant, and whether the pro-tumor effects are mediated by any other TGF-β, other than what species are inhibited by the one antibody that was used. Therefore, while one of skill in the art would know how to use an antibody such as the exemplified antibody that binds to TGF-β1, TGF-β2 and TGF-β3 together with cyclosporine, it would be merely fortuitous if one of skill in the art were to test all of the other antagonists and find ones that would be useful in combination with any other immunosuppressant, and that these combinations would be useful for one purpose that is described in the specification. Thus, further experimentation that is not routine and that would require the discovery of a use for a combination of any one of the many possible TGF-β antagonists and any of the many possible immunosuppressants would be necessary to make and use the claimed inventions.

9. Claims 23, 24 and 25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that the claimed inventions are drawn to compositions comprising any one of a TGF-β1, TGF-β2 or TGF-β3 antagonist in combination an immunosuppressant, whereas the teachings of the specification do not relate to a composition where the antagonist specifically inhibits any one of TGF-β1, TGF-β2 or TGF-β3. Therefore, the description provided by the specification fails to support compositions that are drawn specifically to antagonists that specifically inhibit the activity of any one of TGF-β1, TGF-β2 or TGF-β3.

The support provided in the specification is limited to the description of an antagonist that is a monoclonal antibody that binds to all three molecules, TGF-β1, TGF-β2 and TGF-β3. The specification contains no teachings showing that the effects of cyclosporine are mediated by all three molecules, a particular subset of the three molecules or any one of TGF-β1, TGF-β2 or TGF-β3. Because the experiments shown in the specification demonstrate the effects of an antibody that binds to all three molecules, the experiments do not provide support for compositions that comprise separately any of TGF-β1, TGF-β2 or TGF-β3 in combination with an immunosuppressant. Therefore, one of skill in the art would not find that applicant was in possession of the inventions as claimed.

10. Claims 21 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Dwyer (U.S. 5,238,689; issued Aug. 24, 1993) as evidenced by Cosgrove (U.S. Patent 6,492,325; issued Dec. 10, 2002).

Dwyer teaches methods and compositions comprising the combination of FK-506 (an example of a TGF-β1 antagonist, as evidenced by Cosgrove, col. 19, lines 30-59; and col. 6, lines 1-7) and an immunosuppressant such as Ruthenium Red (see claim 2 of Dwyer). Therefore, Dwyer teaches a composition comprising a TGF-β1 antagonist (FK-506) in combination with an immunosuppressant (Ruthenium Red), and teaches the compositions as claimed.

11. Claims 21-24, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ferguson (U.S. Patent 5,662,904; issued Sep. 2, 1997) in view of Rinehart (U.S. patent 6,156,724; issued Dec. 2000; effective filing date June 7, 1996).

Ferguson teaches methods of wound treatment with neutralizing antibodies to either TGF-β1 or TGF-β2 (see claim 1), and teaches that burn wounds are within the scope of treatable wounds (see col. 1, lines 18-25). Rinehart teaches the use of didemnins in methods for immunosuppression (see claim 1), and specifically teaches the use of didemnins in methods of treating burn wounds (see claim 2). The claimed compositions comprising a combination of a TGF-β antagonist and an immunosuppressant can be viewed as compositions comprising a combination of ingredients known in the art to be useful for the same purpose, i.e. an In re Kerkhoven analysis (In re Kerkhoven, 626, F.2s 846, 850, 205 USPQ 1069, 1072 (CCPA 1980)). The court held that it is obvious to combine two compositions, in order to form a third

composition, when each of the two compositions is taught by the prior art to be useful for the same purpose. The idea of combining them flows logically from their having been individually taught in the prior art (MPEP 2144.06). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a composition comprising a TGF-β antagonist such as an anti-TGF-β1 or TGF-β2 antibody with an immunosuppressant such as a didemnin, because Ferguson teaches that anti-TGF-β1 or TGF-β2 antibodies are useful in the treatment of burn wounds, and Rinehart teaches that dedemnins are useful in the treatment of burn wounds.

12. Claims 21, 23 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolf (Wolf, G. et al., Transplantation, 60(3): 237-241, 1995; abstract only) in view of Ruoslahti (U.S. Patent 6,436,900; issued Aug. 20, 2002; effective filing date Jan. 22, 1990).

Wolf teaches that cyclosporine stimulates expression of TGF-β1, and also causes inhibition of proliferation of cultured muring proximal tumor cells and syngeneic tubulointerstitial fibroblasts. Wolf suggests that the intrarenal synthesis and release of TGF-β1 may play a role in the cyclosporine-induced growth arrest and therefore, might lead to the development of cyclosporine nephrotoxicity that is characterized by fibrosis and atrophy. Ruoslahti teaches methods for the inhibition of fibrotic disease comprising the administration of decorin, a TGF-β1 antagonist (see claim 1; and col. 2, lines 15-24). Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have added a TGF-β1 antagonist such as decorin to a composition comprising cyclosporine for the prevention or alleviation of cyclosporine-induced fibrosis.

13. Claims 21, 22, 23, 27 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolf (Wolf, G. et al., Transplantation, 60(3): 237-241, 1995; abstract only) in view of Dasch (U.S. Patent 5,571,714; issued Nov. 5, 1996).

Wolf teaches that cyclosporine stimulates expression of TGF-β1, and also causes inhibition of proliferation of cultured muring proximal tumor cells and syngeneic tubulointerstitial fibroblasts. Wolf suggests that the intrarenal synthesis and release of TGF-β1 may play a role in the cyclosporine-induced growth arrest and therefore, might lead to the development of cyclosporine nephrotoxicity that is characterized by fibrosis and atrophy. Dasch teaches methods for the inhibition of fibrotic disease comprising the administration of an anti-TGF-β1 antibody (col. 5, lines 33-35). Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have added a TGF-β1 antagonist such as an anti-TGF-β1 antibody to a composition comprising cyclosporine for the prevention or alleviation of cyclosporine-induced fibrosis.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Anne L. Holleran
Patent Examiner
January 2, 2004